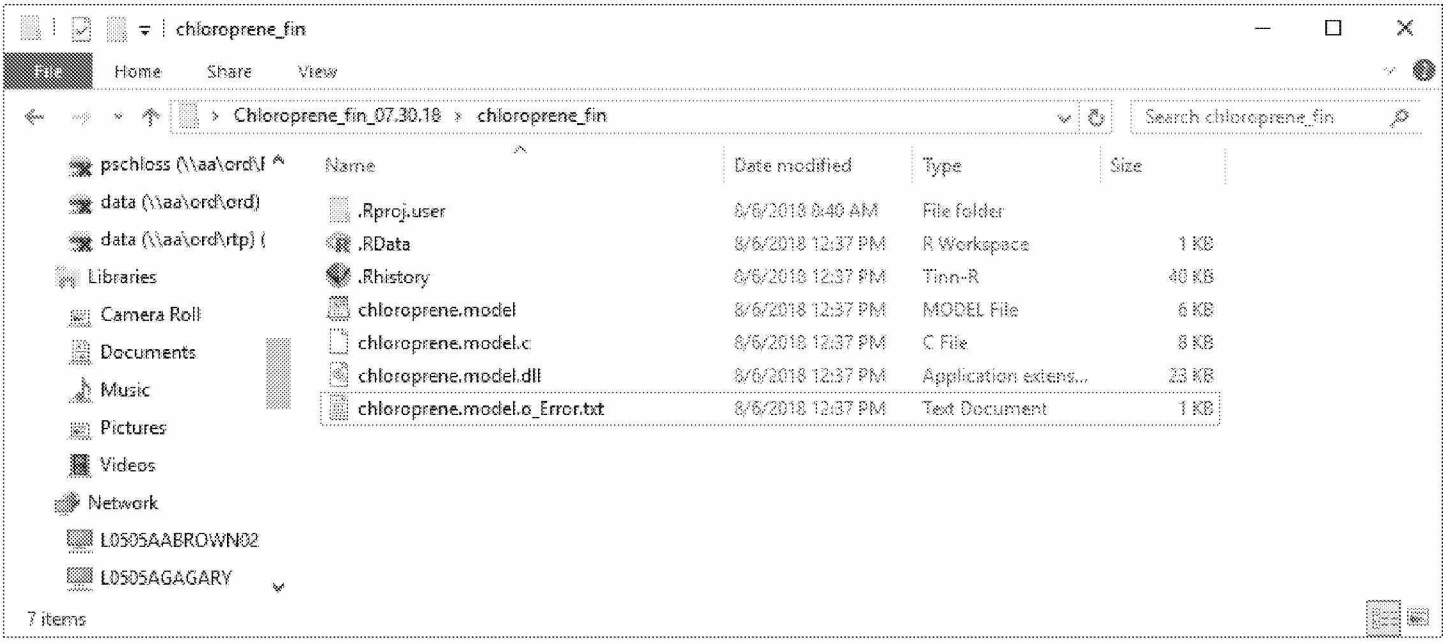

From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Friday, August 03, 2018 2:02 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

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Principal Consultant
1692720 - Tampa

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M +1 (919) 4524279
hclewell@ramboll.com

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Table 1. Tissue: Air Partition Coefficients - Reported in Himmestein et al. 2004; Table 3 CD

Tissue:	B6C3F1 mouse		Fischer rat		Wistar rat		Hamster			Human
Air	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Blood	7.8	0.1	7.3	0.1	8.0	0.5	9.3	0.3	4.5	0.1
Lung	18.6	5.1	13.5	1.6	11.2	0.5	9.7	0.6	13.3	4.095610442
Liver	9.8	0.9	11.5	0.3	10.9	0.2	10.5	0.5	10.7	1.149116225
Fat	135.3	1.6	124.0	1.5	126.3	1.4	130.1	0.9	128.9	2.735761202
Muscle	4.6	0.8	4.4	0.4	4.0	0.3	5.0	0.2	4.5	1.0
Kidney	13.7	0.6	16.7	0.6	9.4	0.4	8.2	0.3	12.0	0.924295154

Table 2. Tissue:Blood Converted Values from Tisse:air PC Tissue:Blood

	Mouse	Fischer rat	Wistar rat	Hamster	Human		
Lung	2.38	1.84	1.41	1.04	2.92		PLU
Liver	1.25	1.57	1.37	1.12	2.35		PL
Fat	17.29	16.87	15.88	13.92	28.38		PF
Muscle	0.58	0.60	0.50	0.54	0.99	Slow	PS
Kidney	1.76	2.27	1.18	0.88	2.64	Rapid	PR

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VMAXCkid set to 0.08, but documentation sheet and Yang et al. (2012) say 0.078. R-script updated to match other info.

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Comments on parameters as listed in "Chloroprene Documentation_08.03.18.xlsx"

Body weights: for mice and rats the information in Brown et al. (1997) (Table 1 and p. 413) gives a wide range. Here it is preferable to use study-specific values (since BW is commonly measured and can vary widely). The values listed are in fact identical to the study-specific values listed by Himmelstein et al. (2004b).

Ventilation and cardiac output: In contrast, it is uncommon for these to be measured. In particular, Himmelstein et al. (2004b) did *not* measure these, but lists them as "based on Brown et al. (1997)." Presumably this means some calculation/conversion, which needs to be shown, or the values updated to ones for which the calculation can be shown.

Alveolar ventilation: converting the values for mice and rats to ml/min/(100g BW) yields values close to but slightly different from the mean values given in Table 31 of Brown et al. (1997) for those species.

For humans the conversion is to within rounding error of the corresponding mean in Table 31 of Brown et al. (1997).

Cardiac output: For rat the QCC and BW yield a total cardiac output of 106 ml/min, close to the mean value in Table 22 of Brown et al. (1997), 110.4 ml/min.

**However, for the mouse the QCC and BW yield a total cardiac output of 36 ml/min, while Table 22 of Brown et al. (1997) gives a mean of 14 ml/min, with a range of 12-16 ml/min. Hence the QCC is unrealistically high, should be ~ 11.7 L/h/kg$^{0.75}$. But using QCC=11.7 in the female_mouse_invivo_3.R script results in significant over-prediction of the blood concentration data. This indicates a failure in in-vitro to in-vivo extrapolation, since the increase in QCC effectively increases the rate of metabolism (when flow-limited) to a similar extent. At a minimum, the "parallelogram" approach suggests that a similar correction, a factor of 2.6 times the mean, should be applied for the human QCC when calculating human internal doses.

QSC: Should be 0.159 for the mouse.

Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/10/2018 9:36:41 PM
To: Jerry Campbell [JCampbell@ramboll.com]
CC: Harvey Clewell [HClewell@ramboll.com]; Allison Franzen [AFranzen@ramboll.com]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]
Subject: RE: transmission of PBPK model for chloroprene
Attachments: Chloroprene param corrections.docx

Jerry, all,

See attached for small discrepancies found and corrections made in comparing parameters in the model scripts to those in the documentation excel sheet. For only these I've checked them against the source publication, to resolve whether the error was in the script or the spreadsheet. The rest of the parameters (taken from prior publications) will still need to be checked against the source documents.

I expect these will only change the dose metrics by a small amounts, but given that those are shown to 3 decimal places, enough to show up.

Alan: please continue to use the parameter files as received in your checking of the dose metrics, so that we know we are getting the same results prior to making these corrections.

As I've communicated to Jerry, I have re-structured the parameter files so that each species has a single 'physiology' script (includes PCs), since all those params are identical between males and females and should be consistent across the metabolic parameter sets. I did ***not*** check that the original sets of physiological parameters were consistent across all 6 rat param files and all 6 mouse param files. For example, Human_5.R now begins:

```
source('./params/Human_phys.R')

parms <-c(parms,
...
```

I've also removed the setting of MW, tstop and conc in these, since those are set in the default parameter array. Adding the function call to initParms in the dose metric scripts assures those are set to the defaults; e.g.

```
source('./params/Female_Mouse_2.R')
parms <- initParms(parms)
```

Have a great weekend!

-Paul

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Sent: Thursday, August 09, 2018 5:47 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
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I can walk you through the forcing function and how it works. I had set it up to be similar to the "schedule" format that was traditionally used in acslX where one would set exposure length and number of days per week to expose. It may be adding complication that is unnecessary for this model where we could switch use events. You can plot the forcing function after running a simulation. The matrix is named signal and there is only one import for this model.

plot(signal$ftime,signal$import1, 'l')

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> rout
   ppm       AMP       AMPLU AMPK
1 12.3 0.2530232 0.04041056    0
2 32.0 0.6581998 0.10513844    0
3 80.0 1.6450145 0.26288161    0
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> rout
   ppm       AMP      AMPLU       AMPK
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3 80.0 2.9397783 0.7104413 0.10875550
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There are no scripts to produce the plots sent by email (via Harvey) on 7/31. We will need them. It would be good to have plots for the kidney data/fits too, though it's a fairly small contributor.

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Unfortunately, I believe that the restrictions are on your end not ours. We can all see the files no problem.

Cynthia

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I tried to just download it. Does it have to be this complicated? We'll be sharing with everyone as part of our open and transparent process…

-Paul

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Thanks, Cynthia

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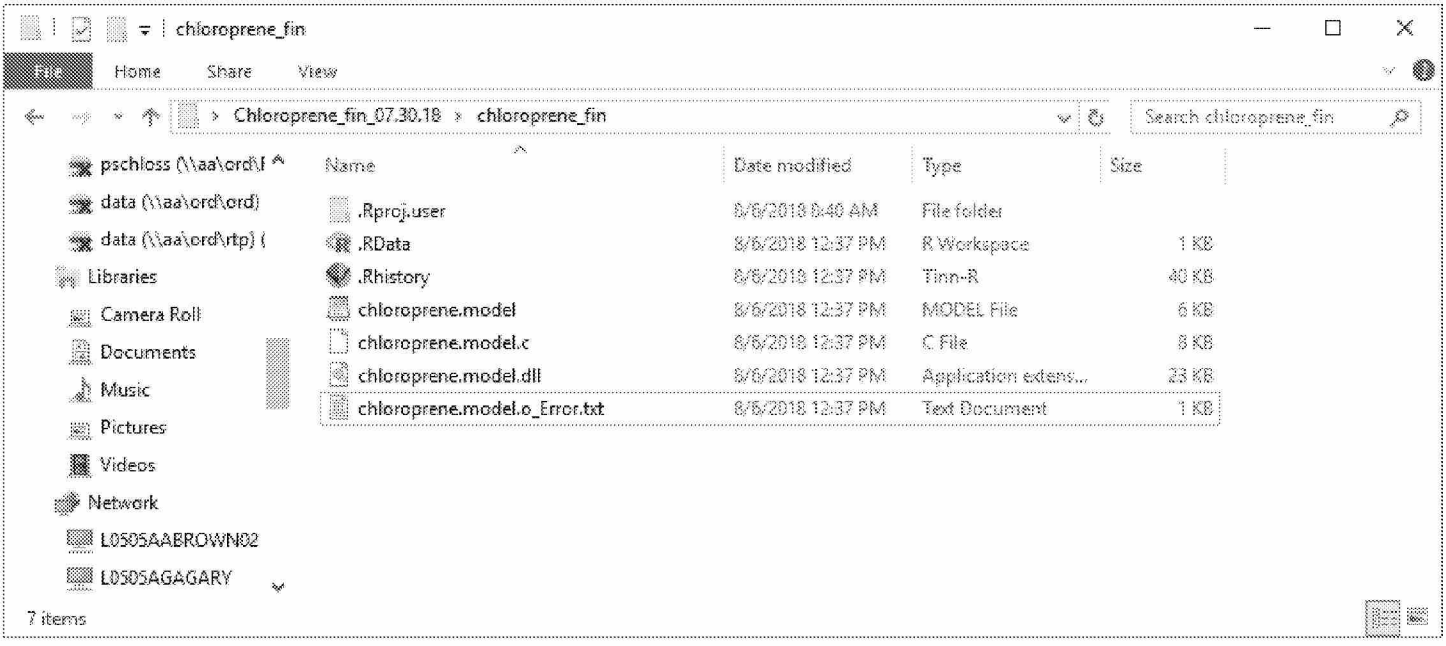
Harvey,

I sent a separate email to Alison. Below is a screenshot of the model folder that I got. There are none of the scripts listed in the Excel 'documentation' file.

Once we have those, give us some time to look at it. Hopefully it's easy enough to figure out, but we can let you and Jerry know if we need a walk-through.

-Paul



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Sent: 8/10/2018 7:50:44 PM
To: Jerry Campbell [JCampbell@ramboll.com]
Subject: RE: transmission of PBPK model for chloroprene

Would have been more efficient, and less possibility of errors, to have a single script for mouse physiological parameters and PCs, that is called prior to setting the different metabolic options. Likewise for rats. I'm also noting that there's no difference in male vs. female physiology parameters for mice or rats. As is I have to check these 6x for each of those species, rather than just once! (I will likely go ahead and make that common script.)

-Paul

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Sent: Thursday, August 09, 2018 5:47 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; cvanlandingham@ramboll.com
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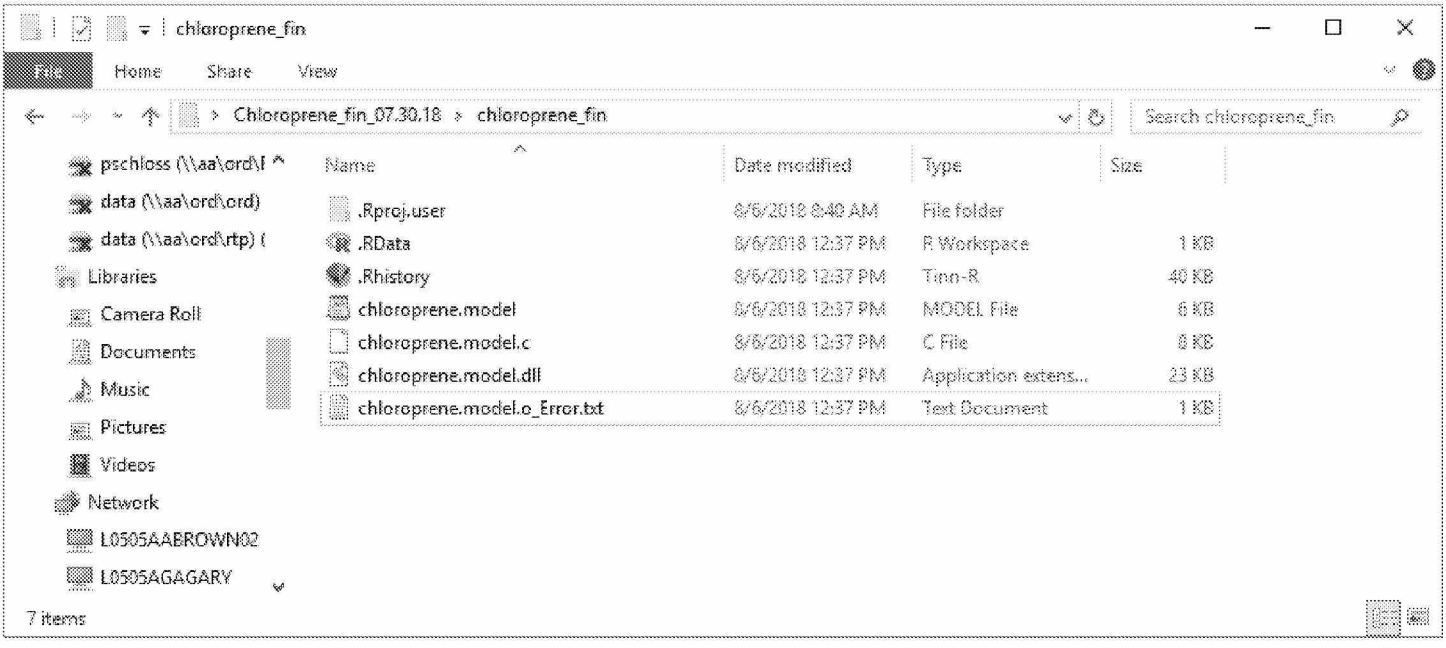
Subject: RE: transmission of PBPK model for chloroprene

Harvey,

I sent a separate email to Alison. Below is a screenshot of the model folder that I got. There are none of the scripts listed in the Excel 'documentation' file.

Once we have those, give us some time to look at it. Hopefully it's easy enough to figure out, but we can let you and Jerry know if we need a walk-through.

-Paul



From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Friday, August 03, 2018 2:02 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

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Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 9/5/2018 7:52:50 PM
To: Jerry Campbell [JCampbell@ramboll.com]; HIMMELSTEIN, MATTHEW W [Matthew.W.Himmelstein@dupont.com]
CC: Harvey Clewell [HClewell@ramboll.com]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]
Subject: RE: Chloroprene In Vitro model

That's a good validation. It may be the difference between the volume to the neck of the bottle and to the very top, what's under the cap. You'd want a "10 mL" vial to hold 10 mL without being full to the tippy top.

BTW, this is from the code on p. 102 of the IISRP-xxx report:

```
VVIALF=0.01165; %% Male ==VVIAL=.0119573;
VVIALM=0.0119573;
VMED=.001;
VINJF=0.0002; %% Male ==VIN=0.0003858 !important
VINM=0.0003858 ;
VAIRF=VVIALF-VMED;
VAIRM=VVIALM-VMED;
```

That's consistent with differences between the 2004 and 2012 papers, but not between volumes in a given study.

The sample volume makes a much bigger difference than the vial volume, but if we're going to the model, I don't want to be trying to explain numbers with higher accuracy than is supported by data for either parameter.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Wednesday, September 05, 2018 3:06 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

The measured total volume of a 20 mL headspace vial is 24.65 mL in Gargas' PC paper so the 10 mL vial is similarly under reported.

Jerry Campbell
Managing Consultant

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jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, September 05, 2018 12:07 PM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt,

Sorry. I was also wondering at the volume being 1.6 mL bigger than advertised, it seemed like a large discrepancy.

A memo is attached, but here is what I've gotten from looking at the code in the appendix of the report you sent:

- Data to indicate that mass transfer resistance is not significant are still lacking.
- The sample volume (VINJ) for all the CP ***oxidation*** experiments in the 2004 paper should be ~ 400 uL, including male mouse and rat liver and lung data. But the code in the report uses 385.8 uL for male data and exactly 200 uL for male data. Is the higher accuracy for the rodent male and human data supported by some measurements?
- Assuming a similar accuracy, the vial volume (VVIAL) for all experiments described in the 2004 paper should be 0.0120 L. This value should be used for male mouse and rat liver and lung data. (We'll use 0.0116 L for the female mouse and rat data and the kidney data.)

Thanks,
-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Wednesday, September 05, 2018 11:01 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

Of course the weight of the vial tared. And I agree the precision defaults to three significant figures, not a total of five.

Matt

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, September 05, 2018 10:53 AM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

Matt,

I'm working on a memo for you, but don't want to get overly nitpicky. This is from the report:

The total volume of Gerstel 10-mL vials used for the incubations was confirmed by gravimetric displacement with water. The measurement was made on 2 occasions once for the liver and lung microsome incubations (n=10 vials) and once for the kidney microsome incubations (n=10 vials). The respective mean (±SD) weights when filled completely with water at room temperature were 11.648 (±0.222) and 11.634 (±0.051) grams. These values were used directly

(without correction for the specific gravity of water) to calculate the corresponding headspace volumes less the 1.0 mL used for the incubation liquid phase.

Now saying that these are the weights "when filled completely with water" indicates that it is the weight of the water ***and*** the vial. Reasonably you would have subtracted the weight of the empty vials, but that's not what it says here.

For the model parameters, this tells me that the measurement precision (or vial volume variance) is on the order of +/- 0.1 g. Hence the volume set in the model code should just be 11.6 mL, assuming that this was after taring.

-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Wednesday, September 05, 2018 8:43 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

Sharing study report from which the manuscript was prepared. Microsomes for in vitro work were purchased or made in house at Haskell.

Matt

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, September 05, 2018 8:16 AM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

Ah. I wasn't sure. The Yang paper says that animals were purchased from Charles River in Raleigh, so I was extrapolating.

-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Tuesday, September 04, 2018 5:08 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

All in vitro incubations were conducted in my lab at Haskell.

Matt

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, September 04, 2018 4:59 PM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

Yes, certainly. I'll send something tomorrow.

I'm presuming that the kidney and female mouse/rat studies were all conducted at The Hamner, so just questions about the 2004 paper.

-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Tuesday, September 04, 2018 4:52 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

Would it be possible to have a word document that categorizes and prioritizes your questions for me?

Matt

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, September 04, 2018 4:26 PM
To: Jerry Campbell <JCampbell@ramboll.com>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

I'm attaching the partial QA tables we (mostly Alan) have developed for the code. The good news is that other than the couple of start-up issues, the in vivo model code is clean, checks out. For the in vitro model we have the assumption of rapid equilibration still to be addressed. There are also a couple of parameter variations/possible discrepancies to be resolved:

VVIAL differs from default (0.01165 L) in the following files:
V_kidney.m (0.01163)
V_human.m (0.0119573)

This seems like it could just be differences in the specific vials/manufacturers, across time and labs, but the value for humans is overly precise, and why would the volume for vials for the kidney experiments be different from other experiments done by Yuching? And why would the volume for the human experiments conducted by Matt differ from

other experiments in his lab? The impact is likely minimal, but in the absence of other documentation, either the default should be used for all experiments or only a Yang-vs-Himmelstein difference used.

As noted in the previous email, we also have that VINJ is set to 0.0003858 L for the human tissue incubations, but 0.0002 L otherwise. The value for humans seems overly precise. How was it determined and why wasn't it exactly 400 uL if other sampling was exactly 200 uL? That Matt changed the sample volume between his human in vitro experiments and rodent experiments needs to be confirmed (Matt, you can just say this in a reply email, if you recall doing that). Otherwise the volume should be consistent with the methods section of each paper: 400 uL for Matt's data, 200 uL for the Yang paper.

The changes/corrections of parameters for the in vivo model will need to be added to the QA table. There were a handful or so of small corrections on which we agreed and the fact that QCC for the mouse is set equal to QPC, which we accept as being consistent with other mouse in vivo data.

We will still need to evaluate the in vivo model against the in vivo PK data from Matt's in vivo paper, accepting that the nose-only chambers likely impacted (reduced) ventilation, but to assure that the model is otherwise consistent with those data. (Reduction in ventilation would not be assumed for open-chamber tox studies, but would be assumed to be independent of exposure concentration for the nose-only studies.) However, we won't attempt that until the in vitro equilibration issue is resolved.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Tuesday, September 04, 2018 12:15 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

I've attached the preliminary in vitro paper mentioned in the email.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, September 04, 2018 8:32 AM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt,

Can you send the 2001 paper, if it shows the rate of equilibration?

-Paul

From: HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
Sent: Friday, August 31, 2018 7:37 AM

To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

Early in vitro work used a Buker shaker the kind of which we also had at CIIT, and was used for 1,3-butadiene in vitro metabolism as well as for all in vitro blood-to-air gas partitioning work pioneered by Gargas at the WPAFB.

We subsequently switched to a Gerstel head space/incubator/mixer auto sampler attached to the HP GC/MSD (see attached photo) http://www.gerstel.com/en/MPS-Agitator-Incubator-Stirrer.htm. All incubations were conducted with a ~1:10 liquid to air ratio (1 mL in 10 mL vial). My understanding is these facilitates rapid equilibration. Any preincubation time was conducted absent metabolizing protein or NADP. A lot of the initial methods were worked out and published in 2001. Sampling at 12 minute intervals was conducted but as I recall, the start times were staggered to fill in for a more continuous curve using multiple incubation vials.

Hope this helps.

I am out of the office today. Back Tuesday.

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Thursday, August 30, 2018 9:54 AM
To: Jerry Campbell <JCampbell@ramboll.com>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

The other possible check is if experiments were run to check linearity of the initial slope with microsome concentration. I'm pretty sure that if mass transfer resistance is at play, you would see a less-than a doubling of the elimination rate when microsome concentration was doubled.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Thursday, August 30, 2018 9:41 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

There were control experiment data in the 2004 in vitro paper – Figure 3A.

Jerry Campbell
Managing Consultant

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jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Thursday, August 30, 2018 9:39 AM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: FW: Chloroprene In Vitro model

Matt,

As a follow-up, see the email from Jerry below… You can follow the thread below that if you wish!

While the question Jerry asks is if you had gentle mixing going on, the information we really need is on the mass-transfer rate under those conditions. Did you ever run control experiments like the plot below, for another chemical if not CP?

Jerry: note that my incubations were also in a shaker, but I think the amount of surface motion would be dampened considerably in a smaller vial.

-Paul

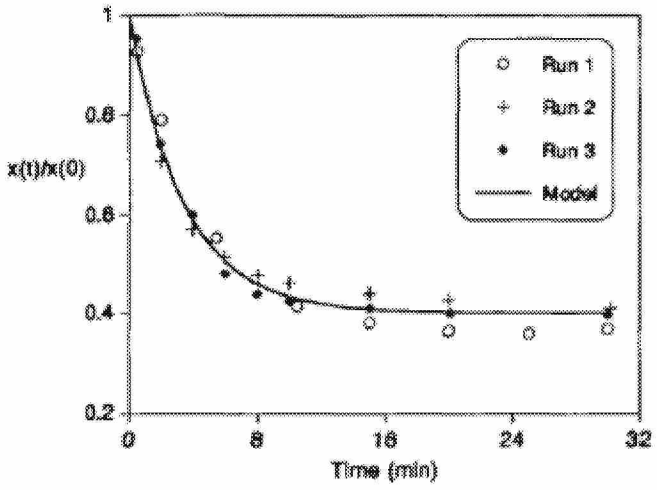


Fig. 3. Partitioning of benzene from liquid phase, into gas phase, in the absence of microsomes under incubation conditions (37°C shaker); $x(t)$ = concentration of benzene in the liquid phase at time = t; $x(0)$ = concentration of benzene in the liquid phase at time = 0. Different initial values, $x(0)$, were used for each run. The model is as depicted in Figure 1 with the rates of biotransformation ($r_1 - r_3$) set to zero.

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Thursday, August 30, 2018 9:10 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>
Subject: RE: Chloroprene In Vitro model

Paul,

Equilibration time question you might want to ask Matt is did they have a shaking sample heater for the headspace vials on their robot? I'm pretty sure they did. The version I had at UGA (was same system sold under another name) had controlled orbital shaking heater that could be set to very slow rotations per min (less than 10/min if I remember correctly) to provide gentle motion. It doesn't say explicitly in the method but it is possible that they used slow rotation to increase surface turnover and decrease liquid equilibration time. We generally used an orbital shaking water bath for non-volatile microsomal metabolism so I wouldn't be surprised if they did include some motion with their analysis too. .

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, August 29, 2018 4:08 PM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>
Subject: RE: Chloroprene In Vitro model

P.S. If there are data for another chemical where the equilibration rate was measured, those could be used with an adjustment of the PC. But it has to be 100x or more faster than what I measured to give results that are indistinguishable from the model where it's assumed to be instantaneous, and that seems unlikely to me.

Or if not, but someone has the system running for other chemicals, it's only a handful of experiments, no tissues.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Wednesday, August 29, 2018 3:17 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>
Subject: RE: Chloroprene In Vitro model

In essence, there was only one sample scheme (every 0.2 hr or 12 min) but I think it may be more complicated than you have coded. It was an automated system – older version of the combi-pal autosampler. In the more highly sampled incubations (2004 paper in vitro paper), Matt reports that up to 5 vials were used to complete a time-course. So, while there was a mass of sample removed at each time, it wasn't linear throughout the whole run. He does state that samples were taken at 12 min intervals which coincides with the 1 vial system data in the female mouse and rat studies. The question is, can we assume that the 0.2 interval samples in the more highly sampled time-course is from a standardized staggered vial system:

Vial 1: 0, 0.2, 0.4, etc…
Vial 2: 0.05, 0.25, 0.45, etc…
Vial 3: 0.10, 0.30, 0.50, etc…
Vial 4: 0.15, 0.35, 0.55, etc…
Vial 5: ???

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, August 29, 2018 2:25 PM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: Chloroprene In Vitro model

Jerry, Harvey,
Cc: Alan, Allen

So I've rigged the code and male mouse liver script to read the sample times from the data file and use those for the "injection" decrement. That should make it easy to apply to other experiments (species/tissues). It also has the separate air/medium compartments. "SET10" gives an initial concentration just in the air phase (I used it to check that the simulations fairly match my old BZ model when I try to simulate that).

I now have it plotting for both variable and fixed Km cases, though the fixed Km value was also hand-adjusted for only the male mouse liver data set. That was partly so I could create an acslX plot definition file (.aps, attached) for the comparison.

The revised .csl, male mouse liver .m file, and .aps are attached. Handling the outputs of multiple lengths is clunky, but as much as I'm willing to do right now.

So the issue as I see it is that one needs to know the mass transfer rate between the gas phase and medium in order to correctly interpret the in vitro data. I had assumed that Matt had done those experiments, included the transfer term, what we learned from working with James Bond. The rate will depend on the surface area in the vial and rate of shaking in the incubator. The rate that I got is clearly too slow to be consistent with the data, but that doesn't mean it's not partially rate-limiting in these experiments. And I don't have a strong intuition for how much it might matter. But the impact will be largest when the rate of metabolism is highest.

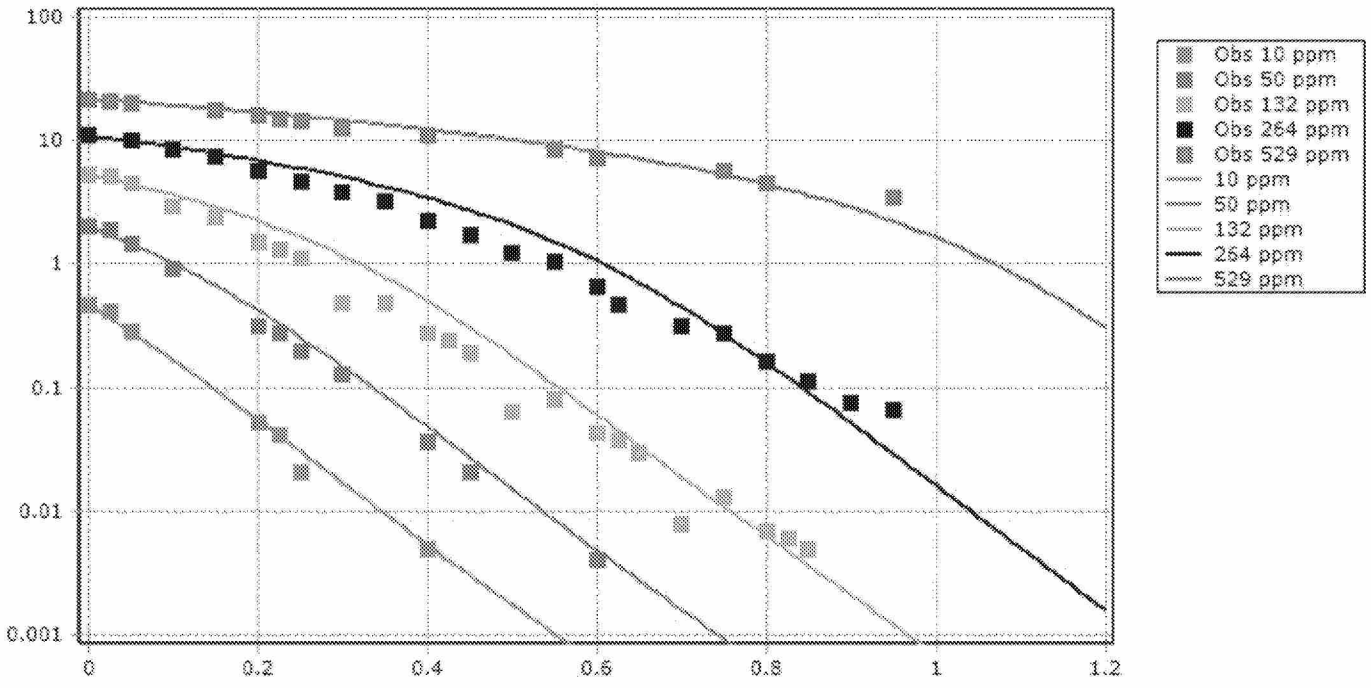
On the other hand, under-counting the sampling (male liver and lung data from Matt) will result in an over-estimate of metabolic rate for those experiments. That will have the largest relative impact when metabolism is slow. At least that just requires an adjustment of the code.

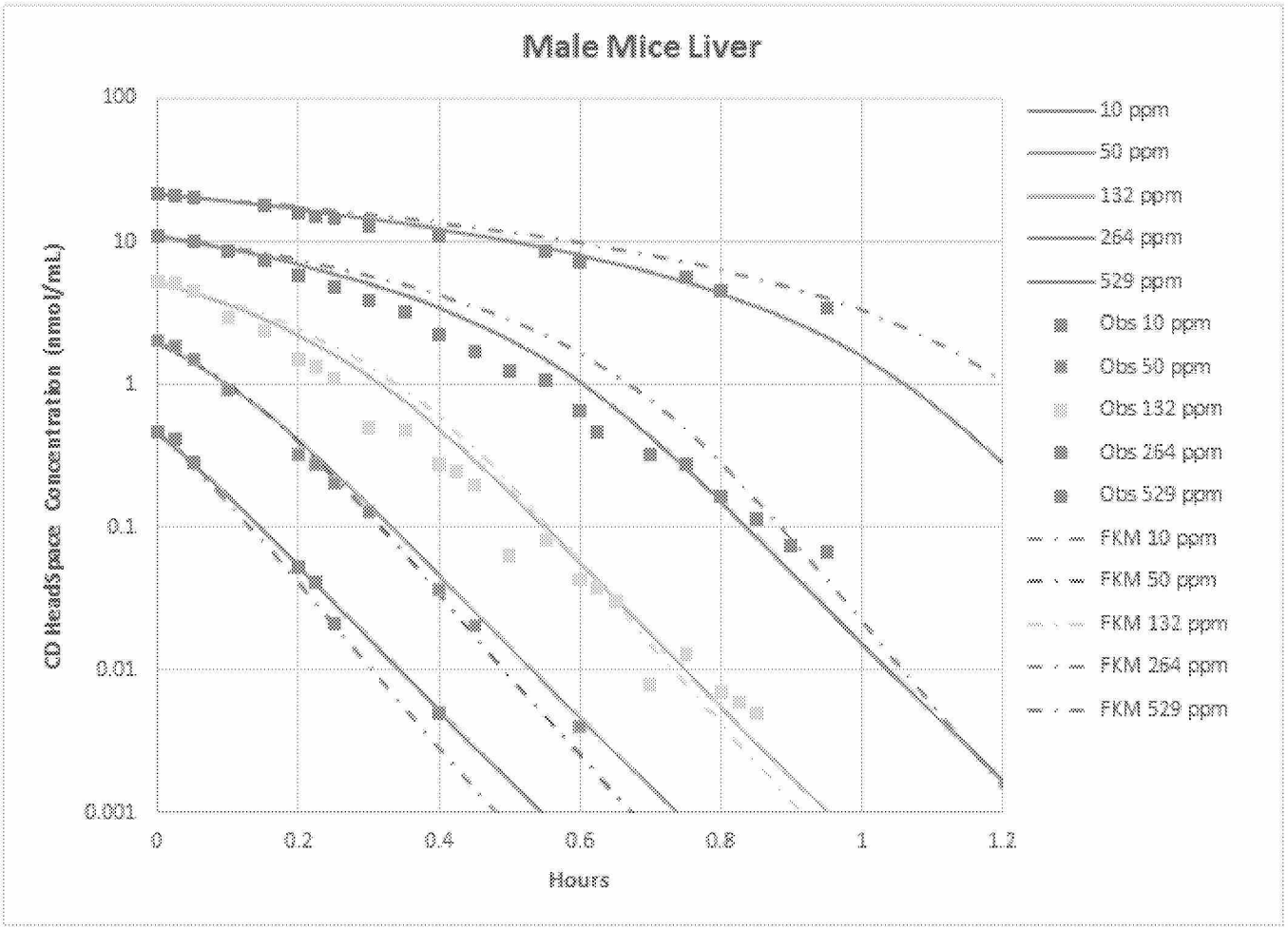
With regards,
-Paul

From: Schlosser, Paul
Sent: Tuesday, August 28, 2018 4:50 PM
To: 'Jerry Campbell' <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

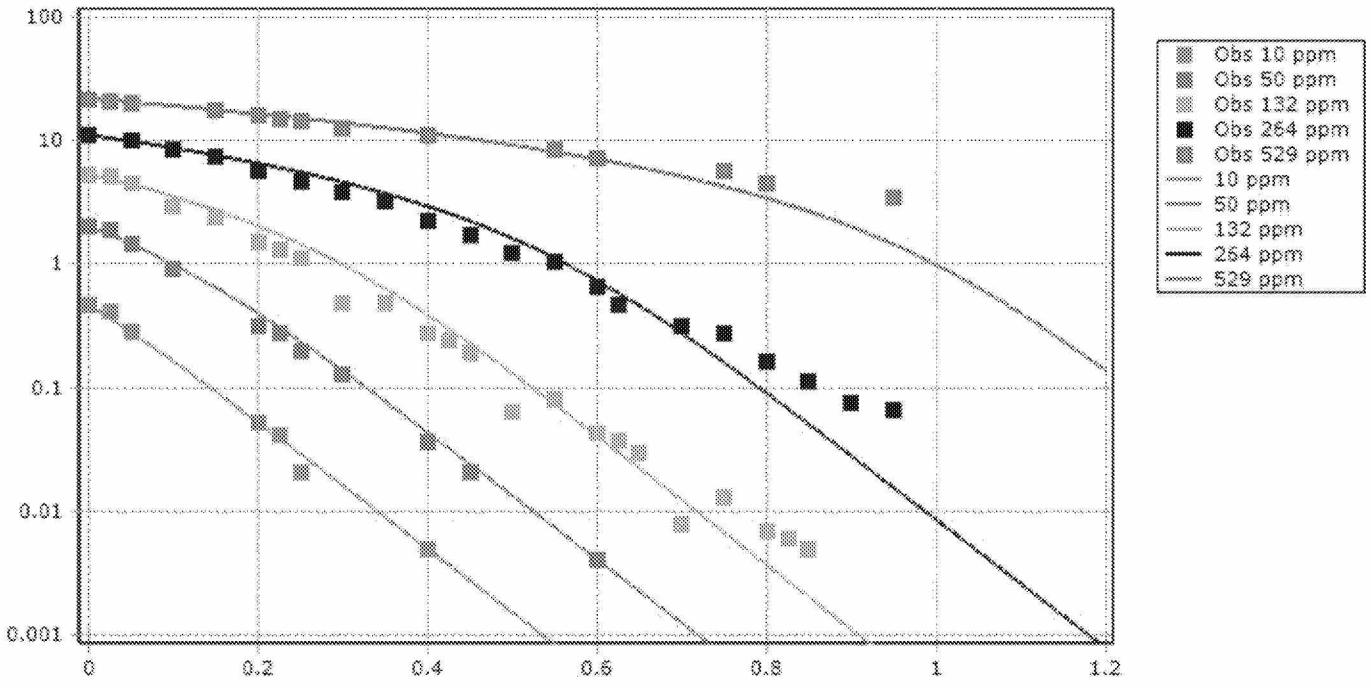
OK, so the first other thing I noticed was that the sampling time (TI) was set to 0.2 h, but clearly samples were taken at a higher frequency. To somewhat quickly get the model to allow for a variation in that, I can't use the procedural, as different sampling intervals changes the length of the output vector, so I can't combine the results in a single array. There's other ways around that, but my cluge was to treat sampling as a continuous loss at rate = VING/TI, where TI is calculated for each data set as TFINAL/NSAMPLE; i.e., the time of the final sample over the number of samples minus the one at time 0.

With the model changed to allow distribution between air and medium (so separate sub-compartments), TI fixed at 0.2 h, but an extremely high mass transfer coefficient (KGL) for air-medium, I get this, compared to the plot (for the Yang parameters) in the spreadsheet that Jerry sent (keep scrolling down):





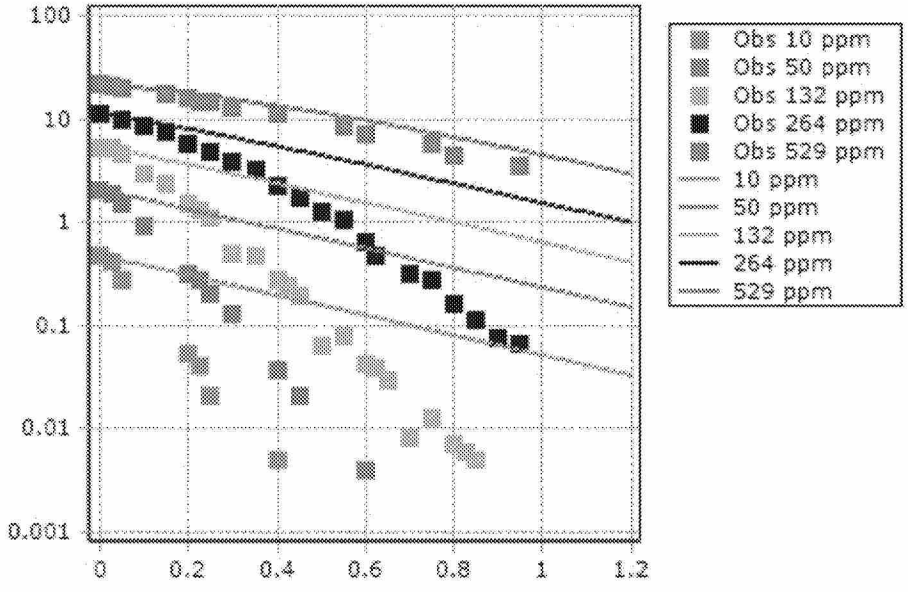
I'd say that's pretty good reproduction! Now, using the variable sampling time (TI), as described above:



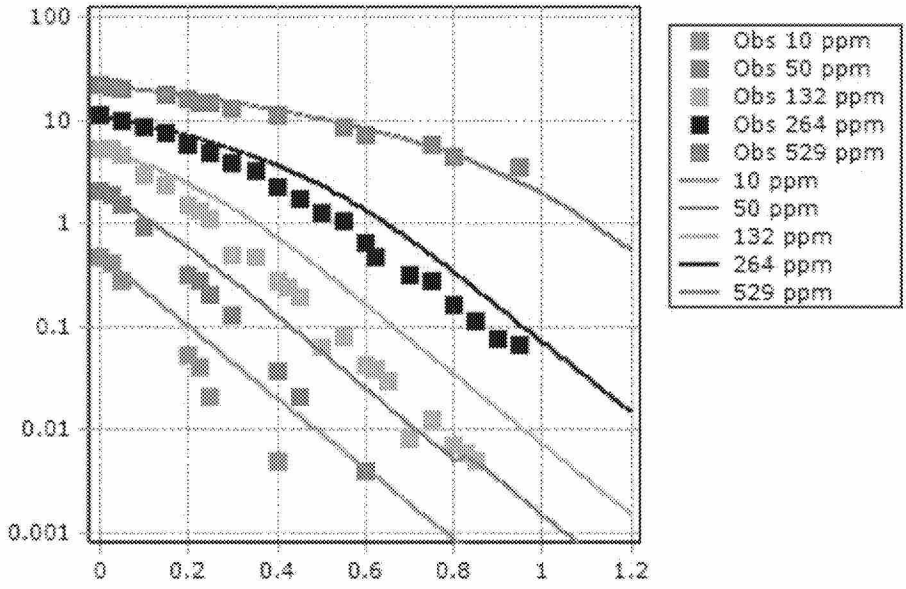
The difference isn't huge, but it's a difference…. For many of the experiments the interval is a fixed 0.2 h, but the male rat and mouse lung, and male rat lung are much more frequent. For the male mouse lung the metabolism is slower, which means the relative impact of this term will be greater.

Ideally the actual sample times should be used, with the scheduled procedural. That's a bit more programming but not terribly difficult. One will just need to deal with the fact that the output from each simulation will be a vector of a different length.

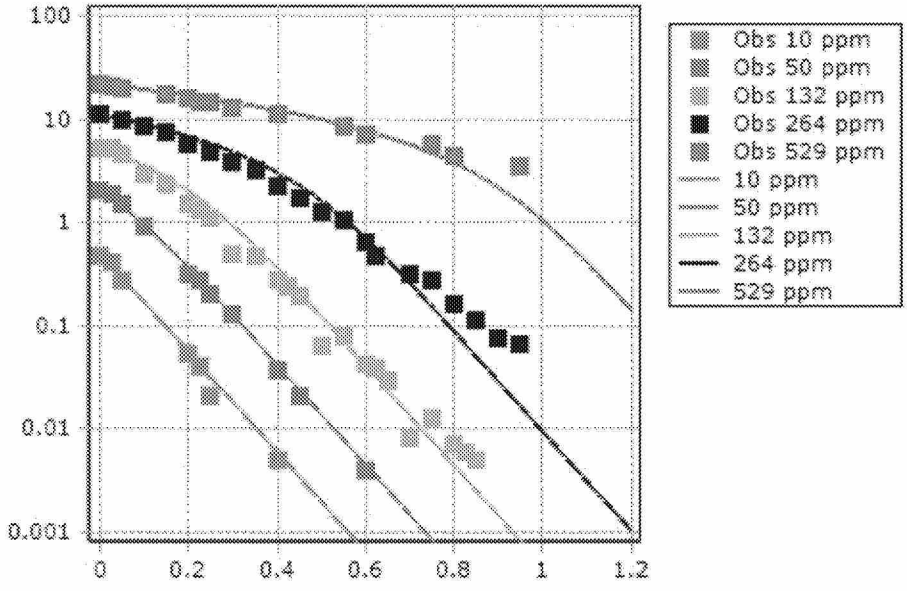
The bigger thing is the gas phase mass transfer. From my '93 benzene paper, the kg = 0.434 ml/min * 60 min/h * 0.001 L/ml = 0.026 L/h. Using that constant, so rate of movement from air to liquid (net) = 0.026*(Ca1 – Cm1/P1), I get:



Really bad, but then there may have been much less mixing in my smaller vials than Matt's, so I increased KGL by 10x, to 0.26:



I then reduced the Km from 1.36 to 0.8 (a bit of trial and error):



Based on this, I'd say that there's a very good chance that the gas-liquid mass transfer is a significant factor, and is likely to impact the estimation of Km (perhaps the goodness of fit of the fixed-Km model). The difficulty is that we need control incubation data to determine the correct value of KGL.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Tuesday, August 28, 2018 11:07 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Yes, it should be +ARLOSS. I must have hit the wrong key yesterday when I noticed it was missing from the equation.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, August 28, 2018 8:42 AM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Thanks, Jerry. I've forwarded to Alan who is getting back to his evaluation of the primary model. I'm hoping we can get through the model code evaluation by the end of next week…

Well, I just looked at the .csl and see this:

```
!MASS BALANCE
  CHECK1 = A10 - (A1+A1M+A1I+ ARLUNGVK-ARLOSS)
```

But that should be +ARLOSS?

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 27, 2018 4:30 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>
Subject: Chloroprene In Vitro model

Paul,

I've uploaded a zip folder (INVITROMODEL AND GRAPHS.zip) with the full workspace for the in vitro model and Excel files with the figures. There is a spreadsheet with a list of the m-files and a short description. Let us know if something doesn't work or you have any questions.

Jerry Campbell

Managing Consultant

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jcampbell@ramboll.com

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Francais Deutsch Italiano Espanol Portugues Japanese Chinese Korean

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Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/10/2018 5:07:10 PM
To: Jerry Campbell [JCampbell@ramboll.com]
CC: Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]; Kapraun, Dustin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3a53c151b92a472fbfb295ed5df982a7-Kapraun, Du]
Subject: RE: transmission of PBPK model for chloroprene

Yes! I owe you a beer!

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Friday, August 10, 2018 12:20 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

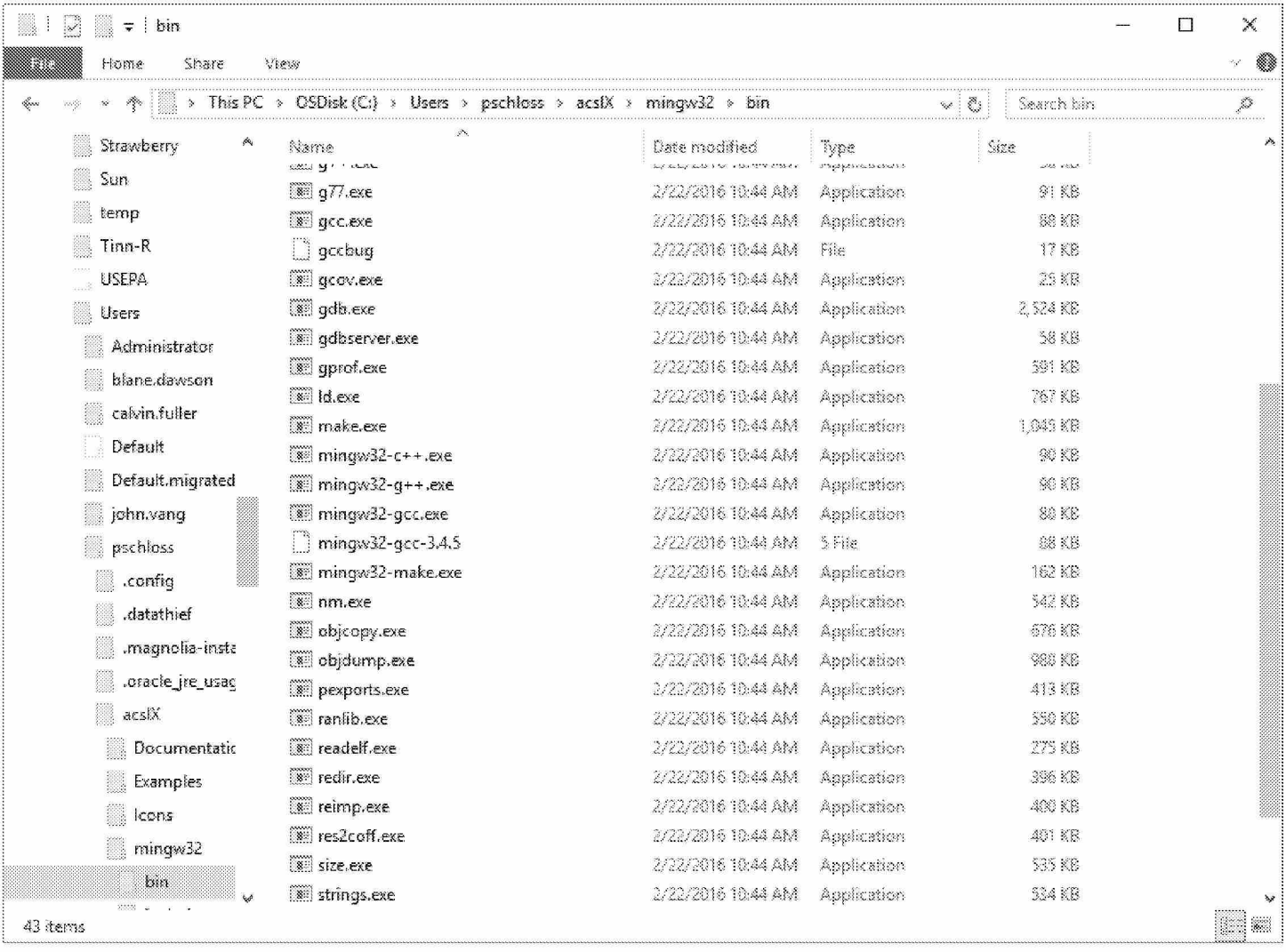
That's it, I'd renamed it already in my folder so I didn't know what the original name was. Change the name or move the old make.exe out of the folder and then delete the mingw32- off that file and see if it helps.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Friday, August 10, 2018 12:17 PM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

Is it the 'mingw32-make.exe'?



From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Friday, August 10, 2018 9:55 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Allison Franzen <AFranzen@ramboll.com>; cvanlandingham@ramboll.com
Subject: RE: transmission of PBPK model for chloroprene

Paul,

Did you try switching to the other make.exe file that is in the bin folder for axslX? There is one that is make.exe, the one you are using, and another one with a slightly altered name. If you switch them so the other one is your make.exe, that had corrected a compile issue we ran into a year or so ago.

Thanks for the dropbox. That should make it easier to transfer files.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Friday, August 10, 2018 8:07 AM
To: Harvey Clewell <HClewell@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>

Cc: Allison Franzen <AFranzen@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Ah, that makes sense. I still have a working copy of acslX, though it's a pain to compile with now: we have to go to a command prompt and manually enter a couple of lines, probably b/c of something that's changed in Windows. Since it's not the primary model I think it's OK to not have it in R.

If you have it compiled, it will save me a bit of trouble. I've sent you and Jerry a DropBox invitation that should work easily, let you just put the files in there!

-Paul

From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Thursday, August 09, 2018 6:26 PM
To: Jerry Campbell <JCampbell@ramboll.com>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Allison Franzen <AFranzen@ramboll.com>; cvanlandingham@ramboll.com
Subject: RE: transmission of PBPK model for chloroprene

Thanks Jerry.

Paul, to get the plots I sent you of the fits to the in vitro data we ran a model of the in vitro metabolism assay, not the PBPK model. The in vitro model is still in acslX – do you need us to convert it to R?

Harvey Clewell
Principal Consultant

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M +1 (919) 4524279
hclewell@ramboll.com

From: Jerry Campbell
Sent: Thursday, August 9, 2018 5:47 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Paul,

Replace the animal scripts with these. Someone, who shall remain nameless, decided to change the simulation to 2 weeks of exposure but set the file to only expose for the first week (dexpend = 5 instead of 12). That's why you get a dose metric that is exactly ½ the table value.

I can walk you through the forcing function and how it works. I had set it up to be similar to the "schedule" format that was traditionally used in acslX where one would set exposure length and number of days per week to expose. It may be adding complication that is unnecessary for this model where we could switch use events. You can plot the forcing function after running a simulation. The matrix is named signal and there is only one import for this model.

plot(signal$ftime,signal$import1, 'l')

Jerry Campbell
Managing Consultant

D 919-765-8022

jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Thursday, August 09, 2018 4:29 PM
To: Jerry Campbell <JCampbell@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Kicking the tires…

I tested a couple of dose metric scripts. The mouse and rat ones I checked seem to produce values ('rout') almost exactly 50% of what's in the 'dose metrics' tab. But the human dose metric script matched.

```
> source('C:/Users/pschloss/Downloads/Desktop/chloroprene_fin/Human_dose_metric_2.R')
> rout
   ppm       AMP       AMPLU AMPK
1 12.3 0.2530232 0.04041056    0
2 32.0 0.6581998 0.10513844    0
3 80.0 1.6450145 0.26288161    0
> source('C:/Users/pschloss/Downloads/Desktop/chloroprene_fin/Male_rat_dose_metric_2.R')
> rout
   ppm       AMP      AMPLU       AMPK
1 12.3 0.4482158 0.1075722 0.06755752
2 32.0 1.1740539 0.2822177 0.09051064
3 80.0 2.9397783 0.7104413 0.10875550
```

There are no scripts to produce the plots sent by email (via Harvey) on 7/31. We will need them. It would be good to have plots for the kidney data/fits too, though it's a fairly small contributor.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 06, 2018 9:30 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; cvanlandingham@ramboll.com; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I was just getting to that option. See if this will work.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 9:26 AM

To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Try just changing the file-extension from .zip to .txt and sending as an attachment. I'm trying to unzip the thing from the sharepoint site and just getting a spinning wheel.

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:19 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Unfortunately, I believe that the restrictions are on your end not ours. We can all see the files no problem.

Cynthia

Cynthia Van Landingham
Senior Managing Consultant

D +1 (318) 3982091
M +1 (318) 6147920
cvanlandingham@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 8:18 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I tried to just download it. Does it have to be this complicated? We'll be sharing with everyone as part of our open and transparent process…

-Paul

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:13 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Paul,
Did you download the zip file to your hard drive and then open or did you open it on the OneDrive site? If you did not try this, selecting all the files and allowing OneDrive to produce one download zip may be best. The chloroprene_model.o_error.txt file is not in the zip we created so may be something that is being created due to the download process. Please read that file to find out if your IT security set-up is preventing files from being extracted.

Thanks, Cynthia

Cynthia Van Landingham
Senior Managing Consultant

D +1 (318) 3982091
M +1 (318) 6147920
cvanlandingham@ramboll.com

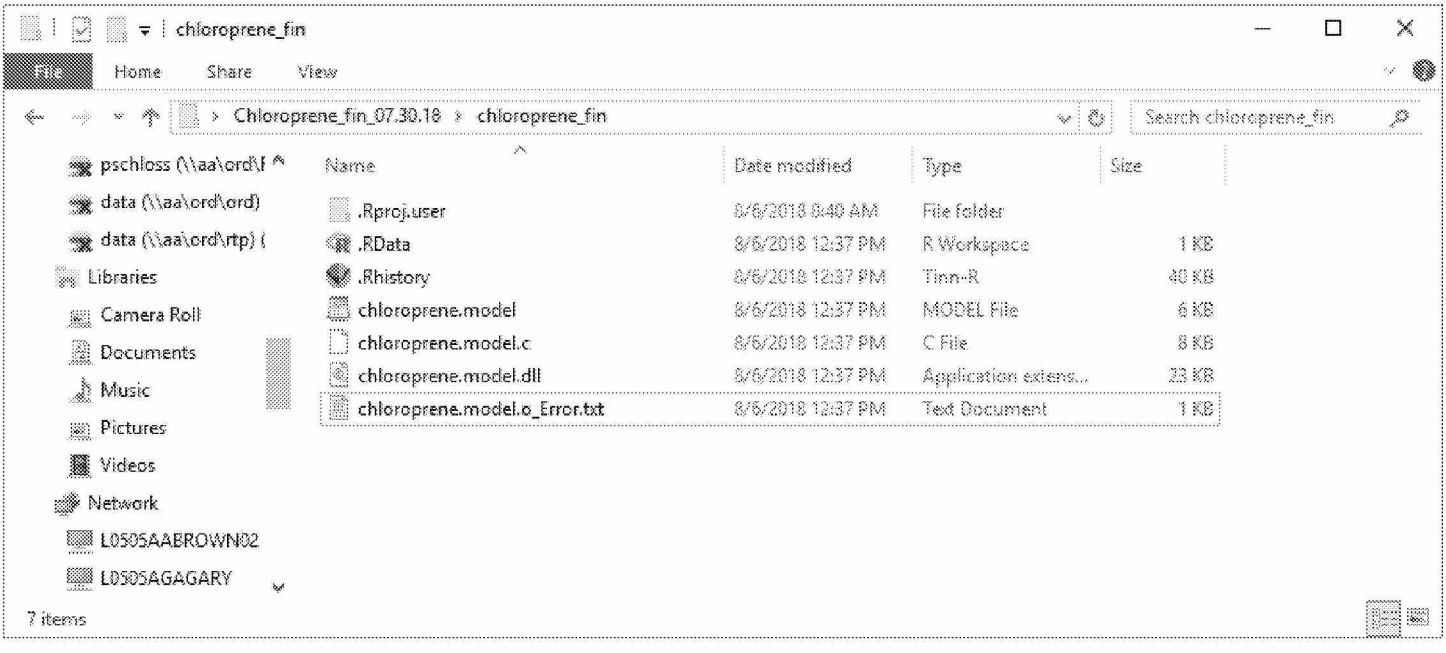
From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 7:53 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Harvey,

I sent a separate email to Alison. Below is a screenshot of the model folder that I got. There are none of the scripts listed in the Excel 'documentation' file.

Once we have those, give us some time to look at it. Hopefully it's easy enough to figure out, but we can let you and Jerry know if we need a walk-through.

-Paul



From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Friday, August 03, 2018 2:02 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

PhD, DABT, FATS
Principal Consultant
1692720 - Tampa

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hclewell@ramboll.com

Connect with us

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PO Box 13441
Research Triangle Park
NC 27709
USA
www.ramboll.com

Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/10/2018 4:59:36 PM
To: Jerry Campbell [JCampbell@ramboll.com]
Subject: RE: transmission of PBPK model for chloroprene

Yes. Look in the dropbox Model_exchange folder.

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Friday, August 10, 2018 12:38 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; cvanlandingham@ramboll.com; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

Paul, I got an unsupported file type on your email. Was the dll file still in the folder? That usually is the culprit.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Friday, August 10, 2018 11:49 AM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

So Dustin set it up in for the sequence of bolus doses in the Greer study for perchlorate using the 'events' input structure. My understanding is that this effectively stops the ode solver at each event, implements the change specified for that event, then re-starts the solver. If you have a parameter that multiplies inhalation concentration that switches 0-1 for off-on, call it inhon, then, then you could have the set of 'on' events and 'off' events which flip it back and forth.

We'd also run each exposure level separately.

See the greer_test.r script in the attached.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Friday, August 10, 2018 10:14 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; cvanlandingham@ramboll.com; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

Paul,

There are quite a few ways in R to input exposure. Most seem a little more cumbersome than acslX but only if you were familiar with the schedule statement in acslX. I have some complex inputs that I actually had to create as csv files and read them in to the simulation which is why I started using a forcing function. You will need more than a few points to run the in vivo simulation. Otherwise, you only need the last value for the average amount metabolized metrics.

I'm not sure what you mean by stopping the simulation. Do you mean setting up every concentration as a separate .in file and then calling them sequentially in R or is there a way to run multiple MCSim inputs directly in a single R script without the .in file? MCsim doesn't allow control of the output matrix name unless you using the Monte Carlo input so I've generally avoided running directly in MCSim unless necessary? Do you have simple example you could share for your schedule setup? It might be an easier way to run these sims since the inputs are relatively defined.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Friday, August 10, 2018 8:31 AM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: transmission of PBPK model for chloroprene

Jerry, others,
Cc: Alan, Dustin

And thanks! Alan Sasso had already gotten most of the way there (identified it as a scheduling issue). So these may provide a good template.... We've been working in the MCSim language, and have some equivalents to the acslX scheduling, but less convenient.

I looked at the actual 'signal' array. Do you really need to set the time-points that closely? Maybe our approach of just stopping the simulation, reset the parameter, starting again isn't so bad!

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Thursday, August 09, 2018 5:47 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; cvanlandingham@ramboll.com
Subject: RE: transmission of PBPK model for chloroprene

Paul,

Replace the animal scripts with these. Someone, who shall remain nameless, decided to change the simulation to 2 weeks of exposure but set the file to only expose for the first week (dexpend = 5 instead of 12). That's why you get a dose metric that is exactly ½ the table value.

I can walk you through the forcing function and how it works. I had set it up to be similar to the "schedule" format that was traditionally used in acslX where one would set exposure length and number of days per week to expose. It may be adding complication that is unnecessary for this model where we could switch use events. You can plot the forcing function after running a simulation. The matrix is named signal and there is only one import for this model.

```
plot(signal$ftime,signal$import1, 'l')
```